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December 23, 2004

Division of Dockets Management (HFA-305)
The Food and Drug Administration
5630 Fishers Lane, room 1061,
Rockville, MD 20852

Re: Docket No. 2004D-0459, CDER. Draft Guidance for Industry on Pharmacokinetics in Pregnancy--Study Design, Data Analysis, and Impact on Dosing and Labeling.

Abbott Laboratories (Abbott) is very pleased to have the opportunity to comment on the **Draft Guidance for Industry on Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling,** published in the Federal Register on November 1, 2004.

We thank the Agency for their consideration of our attached comments. Should you have any question, please contact Thomas Hassall at (847) 421-3518 or thomas.hassall@abbott.com.

Sincerely,

D. L. Sporn

Douglas L. Sporn

2004D-0459 C3

Abbott

December 23, 2004

Comments on
Draft Guidance for Industry on Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling.

Docket No. 2004D-0459

The following comments on the above-mentioned document are provided on behalf of Abbott Laboratories (Abbott).

II. BACKGROUND

Lines 79-81: *"Because of the physiologic changes inherent in pregnancy, the result can be substantial under dosing, or, in some cases, excessive dosing."*

Comment

The draft guidance provides no supporting information for the assertion that under dosing or overdosing may be *substantial* as a result of the physiological changes during pregnancy. It would be useful to include an example of a drug for which clinically significant under-dosing and a drug for which clinically significant over-dosing have been documented as a result of the physiologic changes during pregnancy.

Lines 91-100 provide the following list of some of the physiologic changes during pregnancy that have the potential to alter PK and/or PD of drugs:

- *Changes in total body weight and body fat composition.*
- *Delayed gastric emptying and prolonged gastrointestinal transit time.*
- *Increase in extra cellular fluid and total body water.*
- *Increased cardiac output, increased stroke volume, and elevated maternal heart rate.*
- *Decreased albumin concentration with reduced protein binding.*
- *Increased blood flow to the various organs (e.g., kidneys, uterus).*
- *Increased glomerular filtration rate.*
- *Changed hepatic enzyme activity, including phase I CYP450 metabolic pathways (e.g., increased CYP2D6 activity), xanthine oxidase, and phase II metabolic pathways (e.g., N-acetyltransferase).*

Comment

The list of changes could similarly describe common *differences* in physiological factors that may exist *between patients* in the general population for whom the dosing recommendations in labeling are presumed to apply. It is not clear whether the changes in these parameters in a woman during pregnancy are generally known to be significantly greater than the inter-individual differences one might encounter in the general population. The *need* for PK/PD studies in pregnancy depends on the extent to which the physiological changes lead to *clinically*

meaningful differences in the response to doses of drugs as recommended for the general population.

Lines 102-106:
"A significant amount of pharmacologic research has been conducted to improve the quality and quantity of data available for other altered physiologic states (e.g., in patients with renal and hepatic disease) and for other patient subpopulations (e.g., pediatric patients). The need for PK/PD studies in pregnancy is no less than for these populations, nor is the need for the development of therapeutic treatments for pregnant women."

Comment

The effects of renal and hepatic impairment with respect to dosing requirements are well documented, as is the need for different doses in children and neonates. As noted in the comment above, it would be useful to include some discussion to support the contention that physiologic changes of pregnancy lead to PK/PD changes of a similar clinical significance, or across as wide a range of drug products, as is presented by renal disease, hepatic disease, or as encountered in pediatric medicine. Perhaps, rather than stating that the need for PK/PD studies in pregnancy is no less than for these populations, it would be more appropriate to state that a similar amount of pharmacologic research has not been conducted to provide adequate data on the effects of pregnancy.

III. DECIDING WHETHER TO CONDUCT A PHARMACOKINETIC STUDY IN PREGNANT WOMEN

Lines 123-131:
"Pregnant women may be involved in PK studies if the following conditions are met (45 CFR Subpart B 46.204):

- *Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and*
- *The risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means."*

Comment

45 CFR Subpart B, Section 46.204 lists 10 conditions (a – j), all of which must be met. The guidance quotes (a) and part of (b). For completeness, and to avoid misleading the reader, the second bullet should include the entire quotation from 45 CFR Subpart B 46.204(b), as follows:

- **"The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means."**

In addition, we recommend that the guidance acknowledge that these are just two conditions among others, all of which must be met. The entire list could be provided as an Appendix to the guidance.

Lines 159-166 list situations in any of which the guidance recommends that PK studies can be conducted in pregnant women, as follows:

- *The drug is known to be prescribed in or used by pregnant women, especially in the second and third trimesters.*
- *For a new drug or indication, if there is anticipated or actual use of the drug in pregnancy.*
- *Use is expected to be rare, but the consequences of uninformed dosages are great (e.g., narrow therapeutic range drugs, cancer chemotherapy). Drugs of this type can normally be studied in pregnant patients.*
- *Pregnancy is likely to alter significantly the PK of a drug (e.g., renally excreted drug) and any of the above apply.*

Comment

The last bullet does not appear to be necessary because, if any of the preceding conditions apply, the drug will already be "qualified" for studies during pregnancy. Perhaps a better approach would be to revise this list to state that PK studies can be conducted in pregnant women **"if pregnancy is likely to alter significantly the PK of the drug AND ANY OF THE FOLLOWING CONDITIONS APPLY."** The remaining 3 conditions could follow.

IV. STUDY DESIGN
B. Population PK Design

Lines 230-232:

"The population PK approach can assess the impact on the PK of a drug on various covariates, such as maternal characteristics (e.g., age, gravity, parity, race, weeks or trimester of gestation), concomitant medications, and underlying medical conditions."

Comment

Because the PK of a drug is unlikely to have an impact *on* covariates such as those listed above, we suggest that the above sentence should be revised to as follows:

"The population PK approach can assess the impact OF various covariates, such as maternal characteristics (e.g., age, gravity, parity, race, weeks or trimester of gestation), concomitant medications, and underlying medical conditions on the PK of a drug."

Lines 237-252 appear to suggest that population PK designs are unlikely to be very useful in detecting anything but large PK differences and only then if the studies are large.

Comment

If this is the intent, the disadvantages should be more clearly described. In addition, **lines 249-252** state that *"Some investigators have proposed conducting a population PK study as a preliminary step and to subsequently conduct a standard intensive PK/PD study if the population PK study suggests changes between the pregnant and nonpregnant women."* The guidance should clearly indicate whether the inclusion of that statement represents FDA's endorsement of that approach.

V. OTHER DESIGN CONSIDERATIONS

A. Study Participants

Lines 259-260:

"Study participants should be representative of a typical patient population for the drug to be studied including race, ethnicity, and trimester of pregnancy."

Comment

We recommend that the guidance specifically indicate whether it is necessary to include race and ethnicity representation in the study population if other studies in the clinical development program have revealed no indication of differences in response in the general population on this basis.

Lines 260-263:

"Factors with significant potential to affect the PK of a drug to be studied (e.g., age, weight, diet, smoking, concomitant medications, ethnicity, renal function, other medical conditions) can be considered depending on the pharmacologic properties of the drug."

Comment

The inclusion of multiple factors such as those described would appear to require large study populations in pregnancy PK trials. It would be useful to include

discussion in the guidance if the Agency considers it an unacceptable alternative to control for other factors with significant effects on PK by excluding certain patients from pregnancy PK trials.

B. Postpartum Assessments

Lines 297-301:
"If subjects are breast-feeding during the postpartum portion of the study, the FDA recommends that the study incorporate appropriate safety precautions concerning drug excretion into breast milk and the effects of the drug on the breast-fed infant. The study design should take into account data concerning the pediatric pharmacology and adverse effects of the drug. A lactation study might be performed in conjunction with postpartum sampling."

Comment

We recommend inclusion of some discussion of the factors that should be considered before enrolling women who are nursing into the postpartum portion of a study. As stated (*"If subjects are breast feeding during the postpartum portion of the study...)* there is the implication that all postpartum subjects may be enrolled without regard to nursing status with certain additional precautions implemented for those who are found to be nursing their newborns after enrollment. We also encourage consideration of the inclusion of examples of "appropriate safety precautions" in such situations.

D. Drug Administration

Lines 320-331:
"In single-dose studies, the same dose can usually be administered to all women in the study. Lower or less frequent doses can be considered to minimize fetal risk in pregnant women who volunteer to take the medication for study purposes, even if it is expected to pose minimal risk at standard doses. The dosage regimen can be adjusted based on the best available pre-study estimates of the PK of the drug and its active metabolites and what is known about drug elimination. A concentration-controlled study design or a dosage adjustment based on the patient's response are alternative methods to consider. For example, the study might be conducted to achieve a specific target concentration using therapeutic drug monitoring procedures. When studying pregnant patients who need the study drug, the dose can be modified, either increased or decreased as pregnancy progresses, to achieve the appropriate response (e.g., lowering of blood pressure, or to decrease adverse events such as hypotensive episodes with antihypertensive therapy)."

Comment

This section provides recommendations on a variety of different topics related to drug administration. A bullet format that clearly separates the topics may be a preferable format.

Lines 321-323:
"Lower or less frequent doses can be considered to minimize fetal risk in pregnant women who volunteer to take the medication for study purposes, even if it is expected to pose minimal risk at standard doses."

Comment

Unless specific information is available to suggest that fetal risk is related to the dose or frequency of administration (within the recommended therapeutic regimen for the drug) it may be inappropriate to suggest that reducing the dose or frequency will significantly alter fetal risk. In addition, data from lower or less frequent doses may be difficult to interpret if the drug does not have linear PK.

F. Studies with No Intended Therapeutic Benefit

Lines 359-360:
"It is possible to study drugs that have no intended direct therapeutic benefit to the pregnant woman provided that the risk to the fetus is minimal (45 CFR 46)."

Comment

While it may be possible to conduct such studies and remain in accordance with requirements for human subject protection, we believe that it will prove extremely difficult to enroll such studies.

Lines 368-372:
"Examples of additional safeguards include administering only products with a long or known record of safety in pregnancy, administering products using only a single dose of the drug, using lower doses of the drug, decreasing the number of drugs (probe substrates) used in any study subject, and limiting study participants to pregnant women only in second or third trimester."

Comments

1. For products with a "long or known record of safety in pregnancy," the need for additional PK/PD studies should be seriously evaluated with respect to its impact on the safe and effective use of such products in pregnant patients.
2. It may be inappropriate to consider that the use of single doses or lower doses reduces fetal risk in the absence of evidence to that effect. In addition, data from single or lower doses may be difficult to interpret if the drug does not have linear PK.

G. Pharmacodynamic Assessments

Lines 376-378
"PK studies are usually enhanced by including PD assessments as part of the study. The Agency encourages sponsors to discuss the selection of the PD endpoints with the appropriate FDA review staff."

Comment

Further information on the process and format for holding a discussion with FDA review staff on the selection of PD endpoints should be provided (for example, the type of meeting (A, B, or C), need for conformance with meeting management goals, to whom requests for such discussion should be submitted, timing of requests with respect to date of meeting, appropriate FDA disciplines to be included, and management level FDA personnel to attend).

VII. LABELING

A. Clinical Pharmacology

Comment

The draft guidance recommends including a cross-reference to the "Dosage and Administration" section from both the "Clinical Pharmacology – Special Populations" section and the "Precautions" section of labeling (**lines 473-474**). We recommend also including a cross-reference **from** the "Dosage and Administration" section of labeling to "Clinical Pharmacology" and "Precautions" whenever specific dosing information for use in pregnancy.